



Soluble fractalkine in the plasma of fibromyalgia patients

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ABSTRACT

Fibromyalgia is a form of non-articular rheumatism in which inflammatory cytokines seem to be involved. However, there is still no analytical specific diagnostic criterion for this disease. The aim was to examine a possible role of fractalkine as a biomarker in fibromyalgia. Plasma levels of soluble fractalkine were compared between women diagnosed with fibromyalgia (n=17) and healthy women (n=10) as controls. Fractalkine released by monocytes was also evaluated. Fibromyalgia patients showed lower plasma fractalkine than healthy women. Since most inflammatory pathologies show elevated plasma levels of soluble fractalkine, the results may contribute towards a differential diagnosis for fibromyalgia.

Key words: fractalkine, fibromyalgia, biomarker, chemokine, monocyte.

INTRODUCTION

Fibromyalgia (FM) is a form of non-articular rheumatism defined as the presence of a prolonged history (>3 months) of chronic generalized musculoskeletal pain (Wolfe et al. 2010). There is still no specific analytical diagnostic criterion for this pathology. Among the posited etiologies of FM, special attention has been paid to the hypothesis of the involvement of inflammatory cytokines (Van West and Maes 2001), especially IL-8 (CXCL8) (Ortega et al. 2009, Bote et al. 2012).

Fractalkine (CX3CL1) is a special inflammatory chemokine with chemotactic activity for monocytes, NK cells, and T cells. It also acts as an adhesion molecule for leukocytes (Jones et al. 2012), and is a mediator of pathological pain (Milligan et al. 2008). Evidence has been emerging regarding

its active role in many rheumatic diseases. These include rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, and scleroderma, as well as other diseases associated with systemic inflammation in which it is always found at high levels (Jones et al. 2012). For this reason, the aim of this study was to compare plasma levels of soluble fractalkine in women diagnosed with fibromyalgia when compared with control healthy women.

The subjects of the study were 17 volunteer patients (all women, aged 32–60 years) diagnosed with FM by a rheumatologist (according to the American College of Rheumatology criteria for the syndrome) (Wolfe et al. 2010). The exclusion criteria were: neoplastic disorder (as determined from the patient's medical history); infection; cardiopulmonary, vascular, or other internal medical conditions; and oral or local corticosteroid or anticytokine therapy that might affect cytokine

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levels. FM patients were classified as belonging to the primary group (with no definitive organic factor triggering the syndrome) according to the classification criteria of Müller et al. (2007) – i.e., Group I: FM with sensitivity to pain but no diagnosis of depression or other relevant psychiatric disorder. Ten sedentary healthy women (HW), who had no symptoms of pain or infectious illness at the time of blood sampling, served as age-matched controls (aged 25–55 years). The levels of soluble CX3CL1 in the plasma and in the supernatants of isolated (“Monocyte Isolation Kit II”, MiltenyiBiotec GmbH, BergischGladbach, Germany) cultured monocytes were determined using an enzyme-like immunoassay (RayBio® Human Fractalkine ELISA Kit, RayBiotech, Norcross, USA). Statistical comparisons were done using the parametric Student's *t*-test. The results are presented as the mean (\pm standard error of the mean).

The plasma concentration of CX3CL1 in FM patients was lower than in the HW group ($p < 0.001$; Fig. 1). However, the production of soluble fractalkine by isolated monocytes was not different between FM patients and HW ($p > 0.05$; Fig. 2).

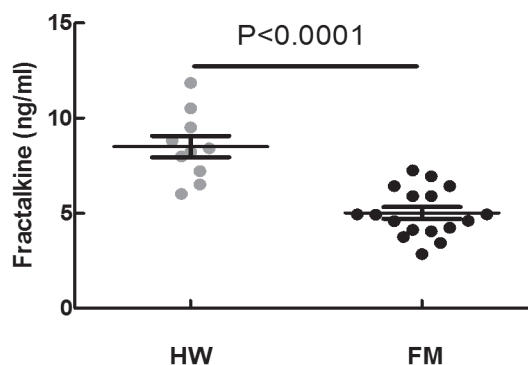


Figure 1 - Plasma levels of soluble fractalkine (CX3CL1) in fibromyalgia patients (FM) and in healthy women (HW). The soluble CX3CL1 level in the FM group was 5.021 (± 0.308 SEM) ng/ml and in the HW group 8.511 (± 0.563 SEM) ng/ml; $p = 0.0001$, Student's *t*-test).

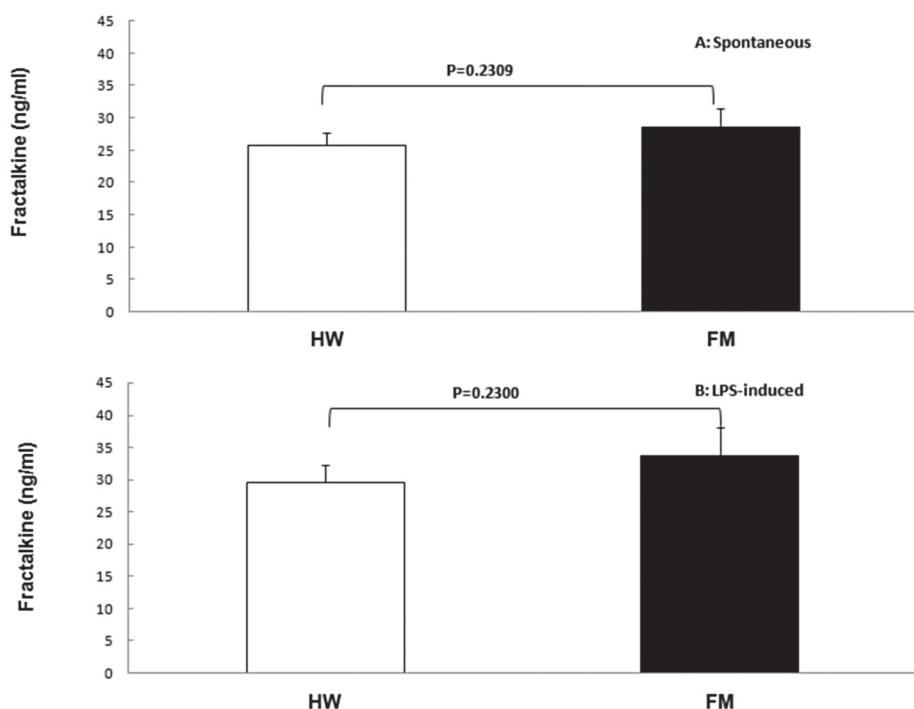


Figure 2 - Soluble fractalkine (CX3CL1) release by non-activated (A: spontaneous) and lipopolysaccharide-activated (B: LPS-induced) monocytes from healthy women (HW) and from fibromyalgia patients (FM). Each column represents the mean \pm SEM of ten experiments performed in duplicate (one experiment per volunteer).

To the best of our knowledge, this is the first study in evaluating fractalkine in fibromyalgia. Soluble CX3CL1 is generated by the limited proteolysis of ADAM ("a disintegrin and metalloproteinase") metalloproteinase domain 10 (ADAM10) and ADAM17 (also called TACE – tumour necrosis factor- α -converting enzyme) (Garton et al. 2001, Hundhausen et al. 2003). This appears to suggest that the lower concentration in the plasma of fibromyalgia patients may be due to a functional defect of ADAM10 and/or ADAM17. However, the capacity of isolated monocytes to produce soluble CX3CL1 was similar in the fibromyalgia patients and in the healthy women, so that, at least in monocytes, it does not seem that the functionality of ADAM10 and/or ADAM17 (which are present in monocytes) is affected in fibromyalgia. Although further studies are needed to clarify the mechanisms underlying the decrease of soluble CX3CL1 in the plasma from fibromyalgia patients; particularly differences in the affinity of fractalkine to its receptor CX3CR1 between FM patients and HW, as well as to evaluate potential changes in the CX3CR1 expression in FM patients. This lower concentration should be another differentiating element between this syndrome and most other inflammatory rheumatic diseases, in which this chemokine is usually increased in plasma (Jones et al. 2012). Then, plasma level of soluble fractalkine could contribute as a biomarker for the differential diagnosis of fibromyalgia compared with other inflammatory conditions.

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RESUMO

A fibromialgia é uma forma de reumatismo não articular, em que as citocinas inflamatórias parecem estar envolvidas. No entanto, ainda não há um critério de diagnóstico

específico de análise para esta doença. O objetivo foi examinar um possível papel de fractalcina como um biomarcador para a fibromialgia. Os níveis plasmáticos de fractalcina solúvel foram comparados entre as mulheres diagnosticadas com fibromialgia (n=17) e mulheres saudáveis (n=10) como controle. Fractalcina liberada por monócitos também foi avaliada. Pacientes com fibromialgia mostraram níveis plasmáticos de fractalcina mais baixos do que mulheres saudáveis. Como a maioria das patologias inflamatórias apresentam níveis plasmáticos elevados de fractalcina solúvel, os resultados podem contribuir para um diagnóstico diferencial para a fibromialgia.

Palavras-chave: fractalcina, fibromialgia, biomarcador, quimiocina, monócito.

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